REMARKS

The claims pending are claims 1, 2, and 4-15. Claims 3 and 16-20 are canceled without prejudice to refiling during the pendency of this application or a continuation application thereof. Applicants further affirm the correctness of the inventive entity in view of the cancellation of claims. No new matter is introduced by this amendment.

Rejections Under 35 USC §112, second paragraph

Claims 1, 11, 12 and 13 are rejected under this paragraph for use of the term "compound". Replacement with 'oligonucleotide' is suggested.

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the above amendments to the claims and the following remarks. The term "compound" has been replace with the term "oligonucleotide' in amended claims 1, 11, 12 and 13. Thus, this rejection may be properly withdrawn.

Rejections Under 35 USC §112, first paragraph

(a) Claims 1, 2, 4-10 and 14 are rejected under this paragraph as containing subject matter not described sufficient in the specification to convey Applicants' possession of the invention at the time of filing.

The examiner cites McLean *et al* **1987** *Nature, 330*:132-137 ("McLean") and Morishita *et al*, **1998** *Circul. 98*:1898-1904 ("Morishita") as presenting the difficulty of using antisense to decrease apolipoprotein (a) because the structure of the latter gene has a high degree of homology to the plasminogen gene, and thus both genes would be inhibited. The specification does not disclose those antisense oligonucleotides that target and inhibit only apolipoprotein (a) not plasminogen, and fails to describe the complete structure of a representative number of species of the claimed genus.

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the above amendments to the claims and the following remarks.

Morishita describes a hammerhead ribozyme for use in inhibiting the Apo(a) gene. The *only* reference that Morishita makes to antisense, are *speculative* statements, such as

> "Although antisense can decrease Apo(a), its application ***may be difficult*** because of very high homology of Apo(a) gene to plasminogen." Page 1898, in the background.

See, also the similar comments in the paragraph spanning col. 2 of page 1898- to col. 1, page 1899, citing McLean. Morishita does not otherwise teach anything specific about antisense sequences and does not teach, identify or suggest any specific antisense sequences that hybridize to Apo(a).

McLean discloses the sequence of cloned human Apo(a) cDNA, and demonstrates that various segments of the Apo(a) sequence show between 78% to 100% sequence homology to plasminogen. McLean says absolutely nothing about antisense sequences. McLean does not otherwise teach, identify or suggest any specific antisense sequences that hybridize to Apo(a).

Applicants' claims 1-11 are directed to compounds that hybridize to, and inhibit expression of Apo(a). These claims require only that the sequences inhibit the expression of Apo(a), regardless of whether they also inhibit another target, e.g., plasminogen. The specification clearly sets out the requirement for the antisense sequences to inhibit Apo(a) and provides sufficient written description to permit one to determine whether or not such sequences do so. See, e.g., the cell assays described in Example 9 of the specification.

With regard to claim 14, which recites a composition containing an antisense oligonucleotide to Apo(a) and a

pharmaceutically acceptable carrier or diluent, the same argument as above applies. Nothing in the claim requires that the compound do anything other than inhibit Apo(a). A full description of carriers and diluents is contained in the specification. Thus, Morishita and McLean do not provide any teachings that challenge the written description of that composition.

Any suggestion by Morishita or McLean that such sequences or compositions may also inhibit plasminogen expression are irrelevant to the written description requirement related to claims 1, 2, 4-11 and 14. The compounds of the present invention are clearly disclosed to have utilities for which any cross-hybridization with plasminogen would not be relevant, e.g., as reagents for research uses. Such compositions and uses are fully described by the present specification.

(b) Claims 15-20 are rejected under this paragraph for failing to enable more than a method of inhibition of the expression of human apolipoprotein (a) in cells *in vitro* using a hammerhead ribozyme targeted to kringle 4 of the human apolipoprotein (a) gene, and fails to enable a method of *in vivo* treatment.

The examiner cites prior art references McLean, Morishita, and Hajjar *et al*, **1996** *Ann. Rev. Medic.*, 47:423-442 as support to indicate that the function of the protein is not understood, and further research is required prior to using therapeutic ribozymes in therapy. The examiner additionally cites the homology with plasminogen and the unpredictability of antisense therapy in general, and the lack of examples in the specification as support for this rejection.

Applicants respectfully request reconsideration and withdrawal of these rejections in view of the above amendments to the claims and the following remarks.

Morishita and McLean are discussed above. Hajjar refers to therapeutic uses of lipoprotein (a).

Cancellation of claims 16-20 render this rejection moot as to them.

Claim 15, as amended, is directed to *in vitro* use of the composition of claim 1 to inhibit *in vitro* expression of Apo(a). Again, claim 15 requires that these compositions inhibit Apo(a). The assays described in Example 9 provide illustrations of *in vitro* assays in which inhibition of Apo(a) by the antisense sequences of this invention can be assessed. The specification fully discloses that the compositions are antisense to, and inhibit, Apo(a) and that such inhibition can occur *in vitro*. It is irrelevant to this claim whether or not the compositions inhibit any other target, such as plasminogen. Hajjar's therapeutic *in vivo* uses for lipoprotein (a) are also irrelevant to this *in vitro* method claim.

Thus, neither Morishita, McLean nor Hajjar provide any teachings relevant to a challenge the written description of amended claim 15. This rejection may properly be withdrawn as against claim 15.

Rejections Under 35 USC §102(b)

> Claims 1, 11, 12, and 15 are rejected as being anticipated by Morishita, cited above. Morishita refers to the phosphorothioate backbone ribozyme oligos, 42-base pairs in length targeted to kringle 4 of the human apolipoprotein (a), which are 80% homologous to plasminogen gene. These ribozymes inhibited human apolipoprotein (a) expression in HepG2 cells, but not plasminogen, and abolished the mitogenic action of conditioned medium in the cells.

Applicants respectfully request reconsideration and withdrawal of these rejections in view of the above amendments to the claims and the following remarks.

As amended, claim 1 (and thus dependent claims 12 and 15) and claim 11 are amended to recite that the compounds are antisense. These amendments exclude the ribozyme sequences of Morishita.

Thus, Morishita does not anticipate the presently amended claims.

Rejections Under 35 USC §103(a)

Claims 1, 2, 4-10 and 12-14 are rejected under 35 USC §103(a) as being unpatentable over the following combination of documents:

(1) Morishita, cited above;

(2) US Patent No. 5,801,154 ("Baracchini"), and

(3) Fritz *et al*, **1997** *J. Coll. Interf. Sci., 195*:272-288.

The examiner describes Morishita as stated above in the prior rejection. The examiner finds that Baracchini refers to modification of oligos; and that Fritz refers to an antisense oligo in a carrier including a colloidal dispersion system. One of skill would have been motivated to make Applicants' molecules using Morishita's ribozymes as a template, modify them as taught by Baracchini and prepare pharmaceutical compositions as taught by Fritz. The examiner finds the invention to be *prima facie* obvious.

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the above amendments to the claims and the following remarks.

As discussed above, Morishita refers to ribozymes that inhibit Apo(a). Such ribozymes are not encompassed by Applicants' amended claims. Moreover, Morishita does not otherwise teach anything specific about antisense sequences to Apo(a), and does not teach, identify or suggest any specific antisense sequences that hybridize to Apo(a). In fact, Morishita explicitly teaches away from the concept of antisense sequences to Apo(a) as having any use, even if made. See, the paragraph spanning col. 2 of page 1898- to col. 1, page 1899.

The two cited secondary documents teach nothing regarding human apolipoprotein (a) or antisense sequences capable of inhibiting human apolipoprotein (a) activity.

Baracchini refers to antisense compounds that modulate another *completely unrelated protein* to human apolipoprotein (a), namely multidrug resistance-associated protein (MRP). Fritz refers to cationic nanoparticles as a carrier system for antisense nucleotides in general.

These references do not teach or suggest any antisense sequences to human apolipoprotein (a) or to any portion of human apolipoprotein (a). The combination of Morishita with Fritz nor Baracchini does not provide any suggestion that suggests compositions containing antisense sequences to human apolipoprotein (a). In fact, neither Fritz nor Baracchini teaches or suggests a utility for antisense compounds that bind human apolipoprotein (a). Morishita speculates that there is no utility!

Thus, this combination of references teaches away from, rather than suggests, the compositions and methods of the claimed invention. The only motivation to make such an invention is derived from Applicants' disclosure.

In view of the above amendments and these remarks, Applicants' respectfully request that the examiner withdraw the outstanding rejections and permit the above pending claims to pass to issue in due course.

The Director is hereby authorized to charge any additional fees required with the filing of this paper or credit any overpayment in any fees to our deposit account number 08-3040.

Respectfully submitted,
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